HUMAN DRUG CGMP NOTES

(Volume 2, Number 4)

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(A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)

Issued By: The Division of Manufacturing and Product Quality, HFD-320
Office of Compliance
Center for Drug Evaluation and Research

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FAX FEEDBACK
(Your input requested)

MOTISE'S NOTEBOOK:

Welcome to another edition of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. Your FAX FEEDBACK responses continue to be excellent and we especially appreciate your suggested topics for coverage. You need not, however, limit the dialog to FAX FEEDBACK. Feel free to call, write or send us e-mail, as several of you have done. We also welcome brief articles FDAers may wish to contribute. (For instance, this edition includes a reviewer's perspective on the first two policy questions which we addressed in our prior edition.) Subjects should be CGMP related and would be especially valuable if they address emerging new technologies.

As a reminder, although the document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is FDA field and headquarters personnel. Therefore, for now, we cannot extend our distribution list to people outside the agency. The primary purpose of this communication is to enhance field/headquarters communications on CGMP policy issues and to do so in a timely manner. This document is a forum to hear and address your CGMP policy questions, to update you on CGMP projects in the works, to provide you with inspectional and compliance points to consider Not in every case. The September Human Drug CGMP Notes states that CDER has performed an intensive evaluation of Millipore's matrix procedures and reports. We are in basic agreement with the matrix concept but we have not performed an intensive evaluation of their matrix procedures and reports. I should point out that Millipore has generated this information for the Durapore filters only. We have seen Millipore's summaries (charts, graphs, etc.) of that will hopefully be of value to your day to day activities, and to clarify existing policy and enforcement documents.

We intend to supplement, not supplant existing policy development/issuance mechanisms, and to provide a fast means of distributing interim policy.

Appended to each edition of the memo is a *FAX FEEDBACK* sheet to make it easier for us to communicate. In addition to FAX (at 301-594-2202), you can reach the Policy and Guidance Branch, HFD-323, by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by electronic mail (under the integrated e-mail system, address the message to the last name of the contact, such as CRABBS, or MOTISE.)

If you would like to receive an electronic version of this document via electronic mail, let us know (see the check off line in FAX FEEDBACK).

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Can manufacturers use Millipore's "Matrix Approach" to validate a product/filter combination as sterilizing? (An NDA reviewer replies to this question, posed in our last edition.)

References: See 21 CFR 211.113, Control of microbiological contaminants

their data but we have not had the opportunity to examine Millipore's actual data. Additionally, we do not have information regarding the design of the studies, the filtration methods used (was the microbial challenge in the actual product or was the product circulated through the filter first), microbial methods, sensitivity of the methods, volume of "reference product" filtered, how much data was generated, how many lots of filters were tested with each of the matrix products, the

composition of the products in the matrix, etc. We have requested that Millipore provide this information in their Master File so that we may reference it in connection with reviews of drug applications. To date, we have not heard from Millipore regarding this request. Additionally, there are products that fall within Millipore's matrix which are not rendered sterile when filtered through the 0.22 micron filter. The matrix may be applicable to some products and we also agree with filter validation for groups of products. However, since there is the possibility that the drug product may cause a reduction in the size of the micro-organisms, it is best to test the microbial retentivity of the filter with the microbial challenge in the actual drug product. In cases where the drug product has antimicrobial properties, a master product can be used which does not contain the antibiotic but otherwise has the same composition and chemical properties as the drug product (ionic strength, osmolarity, pH, viscosity, surface tension, etc.). The bottom line is that the matrix approach is not the automatic solution to filter validation for every drug product. Careful consideration should be given to the drug product and its chemical/physical properties in determining how to correctly validate the microbial retentivity.

Contact for Further Info: Patricia D. Leinbach, HFV-143, 301-594-1672

Does a manufacturer need to test each drug product for filter extractables? (An NDA reviewer replies to this question, posed in our last edition.)

References: See 21 CFR 211.65, Equipment Construction.

It depends on the manufacturing process. Although the September Human Drug CGMP Notes stated that drug manufacturers do not have to test sterile drug products for filter extractables, whether or not a drug manufacturer would have to test for filter extractables depends entirely on the manufacturing process used. If the product is produced by direct in-line filtering and filling, extractables would be a problem in some number of the first containers filled (depends on container size). If, however, the entire batch is filtered into a holding tank prior to the filling operation, extractables may not be a problem but that decision is made by the (new drug application) reviewer and is based on knowledge of the entire manufacturing process. If products are manufactured by a process which allows for (1) recirculation of the product through the filter after integrity testing, or (2) filtration into a surge tank (less than batch size) after filter integrity testing, extractables may not be a problem. Again, this decision is made by the NDA reviewer and is based on knowledge of the entire manufacturing process. When processes that employ recirculation and surge tanks are used, the homogeneity of the product (from first to last container) must be demonstrated. We have also asked Millipore for information regarding the identification of the filter extractables. To date, we have not received this information. The testing that has been done on the gravimetric extractables is the acute toxicity test but to my knowledge the carcinogenicity of the extractables has not been addressed. The first step would be to identify the substances that are extracted from the filters.

Contact for Further Info: Patricia D. Leinbach, HFV-143, 301-594-1672

What stability data is required in a new drug application supplement involving a change in packaging site, considering there will be no changes in the container-closures that will be used to package drugs at the new site?

Reference: 21 CFR 211.166, Stability testing.

Generally, filling tablets or capsules into bottles in a new facility should not affect the stability of the products. However, filling tablets or capsules into blister packaging may present more of a concern than packaging into bottles, therefore requiring more extensive stability data.

A firm may demonstrate that a change to a new packaging site does not significantly affect the stability of its products by demonstrating through stability studies on its most sensitive drug products that the change has no effect. Additionally, bracketing and matrixing may be appropriate in certain situations where multiple strengths of products are packaged into various package sizes and package types. We recommend that application holders obtain specific guidance from the appropriate review divisions on the extent of the stability data needed.

Division Contact for Further Info: Barry Rothman, HFD-325, 301-594-0098

What quality standard should be set for air around a capsule repacking machine where the capsules contain alpha blocker drugs?

References: 21 CFR 211.42, Design and construction, and 211.46, Ventilation, air filtration, air heating and cooling.

We've had similar inquiries before and, unfortunately, there is no set answer. The key is to identify the most significant potential problem. Particulates and microbial counts, of course, need control in a "clean room" environment, where sterility must be preserved. In the case described, however, more important than air quality itself, in terms of particulates and microbial content, would be the matter of dust removal and containment to prevent cross contamination. We would not expect particle counts, per se, to be as important as what those particles are, and the danger they may present if they found their way into other products. Temperature and humidity controls may also be warranted to ensure capsule integrity and the smooth operation of the equipment.

Gas What? (Policy Questions on Medical Gases):

1) What are the requirements for standard reference gases that are to be used in the calibration of oxygen analyzers?

Reference: 21 CFR 211.194(c), Laboratory

A severe cross contamination problem, such as we encounter in penicillin production would warrant separation of facilities: dedicated equipment and air handling systems, along with separation of personnel. As part of future CGMP revisions, we are reviewing the need to extend the penicillin separation provisions to other drugs that might pose unique health hazards. Nothing has been firmed up yet, but the concept is under review. Until the regulations are modified, we would advise the firm to evaluate the potential cross contamination problem, and design an environment and containment provisions that would avoid putting other products at risk.

Division Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089

Is roll labeling that contains splices considered to be cut labeling?

Reference: 21 CFR 211.122(g), Materials examination and usage criteria.

No. The simple answer is that cut labeling refers to individual pieces of labeling in stacks, bundles, or boxes and not to labeling that is attached to other labeling on a roll. Most, if not all, roll labeling contains splices. This is due to the fact that roll labeling is printed on large reels of paper stock on which 6 to 12 labels may be printed side by side at one time; the large roll is then cut into reels one label wide and those rolls are then spliced together to form a larger roll of labeling. The only time that roll labeling becomes cut labeling is when the user cuts individual pieces of labeling off of the roll for application to the container. This occurs quite often in the medical gas industry, for example.

Division Contact for Further Info: Anthony Lord, HFD-322, 301-594-0095

Records

All calibration gases should be purchased from a specialty gas manufacturer and backed up by a certificate of analysis (COA). Note - this COA is not required to provide the air liquefaction statement, since the calibration gases are not medical products.

Recent problems encountered at several filling firms supplying standard reference gas has prompted a change in policy. The problems observed ranged from inadequate testing, inadequate calibration of the analyzers, to inadequate calibration standards.

2) What training is acceptable for the filling of medical gases?

Reference: 21 CFR 211.25(a), Personnel Qualifications

This is one of the most neglected CGMP violations noted in the industry today. While it is acceptable for a firm to provide on-the-job training, the individual(s) responsible for providing this training should be knowledgeable either through education, training, or experience. We expect the on-the-job training to be provided at frequent intervals. Likewise, it is important that CGMP training be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with the CGMP requirements.

This training should be addressed in sufficient detail in the firm's training protocol or procedures, and should be documented.

Division Contact for Further Info: Duane Sylvia, HFD-322, 301-594-0095.

Published In Final:

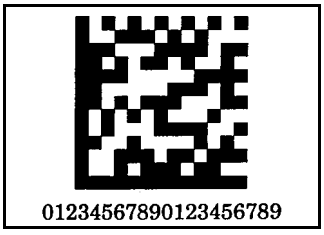
***ICH Guideline, "Stability Testing of New Drug Substances* and Products": Notice of Availability published in the Federal Register of September 22, 1994**

Reference: 59 FR 48754, No. 183, September 22, 1994

This guideline was developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH guideline contains the mutually acceptable stability testing requirements for a registration application (New Drug Application) within the European Community, Japan, and U.S. The stability testing conditions in the ICH guideline differ significantly from those conditions specified in guidelines previously issued by FDA. As mentioned in the FR notice, sponsors submitting future NDAs may be asked to explain any differences from the approach taken in the ICH guideline.

Investigators should be aware that because the document is a guideline rather than a regulation, deviations from the document are not necessarily appropriate as 483 objectionable conditions. The ICH guideline pertains to new molecular entities, not to ANDAs. Additionally, the FR Notice mentions that FDA intends to update its 1987 guideline entitled, "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" to incorporate the new elements in the ICH guideline and other changes in stability testing that have occurred since 1987. Until the 1987 guideline is updated, FDA intends to provide both the ICH guideline, and the 1987 FDA guideline, when information pertaining to stability testing is requested.

Copies of the Federal Register Notice containing the ICH stability guideline can be obtained by contacting CDER's Executive Secretariat office, (301) 594-1012.



Division Contact for Stability Matters: Barry Rothman, HFD-325, 301-594-0098.

New Technology Report:

Data Matrix Codes and Rare Earth Phosphors as Labeling Control

Investigators may encounter firms using data matrix codes instead of the more familiar bar codes. Data matrix codes resemble small

checkerboard squares. (See Figure 1 for an enlarged example.) The data matrix codes are read by a camera instead of the laser scanner used for bar codes. The code can be made much smaller than a bar code and yet contain more information (up to 500 characters in a .05 square inch area). Code may be visible or invisible (invisible code in ultraviolet ink is read with a UV sensitive camera). The data matrix code is in binary code (machine language) and employs NASA developed algorithms for reliable data transfer, using 16 bit or 32 bit cycle redundancy checks (CRC). The small size of the code will facilitate its use on ampules, vials, and syringes. It should be particularly useful in controlling filled but unlabeled containers (bright stock) in that containers could be individually identified using a simple ink jet system before storage and then individually verified when labeled and packaged.

Another technology which we have learned about recently involves the use of rare earth phosphors which emit a specific radio frequency signal when stimulated with a laser. This technology will allow the phosphors to be incorporated into the inks used in printing the labeling. The coding will be non visible, saving space on the labeling for text, and will allow for automated verification of the correct labeling by means of a laser scanner in combination with a radio frequency receiver on the packaging line.

Division Contact for Further Info: Anthony Lord, HFD-322, 301-594-0095

Toward The Electronic Government:

Proposed Rule on Electronic Records/Electronic Signatures Published

Reference: Federal Register, 59 FR 45160, No. 168, August 31, 1994.

Nicknamed the Omnibus Rule due to its agency wide scope, the proposed rule on electronic records and electronic signatures was published in the Federal Register of August 31, 1994. The purpose of the proposal, which calls for a new Part 11 in 21 CFR, is to promote and accept new technologies while maintaining the integrity of the agency's enforcement activities. As we go to press, the comment period is scheduled to end on November 29, 1994.

The proposal moves us closer to the "electronic government" in several ways. First, when a final rule goes into effect, firms could use electronic records in place of paper records and electronic signatures in place of handwritten signatures for records they maintain under 21 CFR provided they follow the new Omnibus rule, and no subsequent regulation dictates otherwise. For records that are submitted to FDA, like NDAs, firms could use electronic records/electronic signatures if the type of submission is identified as one the agency accepts in electronic form--that acceptance would be detailed in a special public docket in which each FDA receiving unit would state the records it would accept along with the submission logistics.

Field investigators should be aware that the proposal places heavy emphasis on maintaining our ability to inspect and copy records (including copies in electronic form). Firms are encouraged to contact their local district offices to determine field local investigator capabilities. In addition, districts would receive firms' electronic records/signature certificates -- affirmations that electronic signatures are equated by firms with handwritten signatures. The certificates would be kept on file should they ever be needed in litigation.

The proposed rule also moves toward the electronic government in that, as an experiment, the agency is accepting comments on the proposal by electronic mail (address 92N0251@A1.FDAOC.FDA.GOV). Furthermore, the text of the Federal Register notice is available by sending e-mail to the Internet address DOC00001@FDACD.BITNET. The text of the notice is also posted on CDER's Internet FTP (File Transfer Protocol) Server, address CDVS2.CDER.FDA.GOV, in ASCII and WordPerfect 5.1 formats, as files ESIGFR94.TXT and ESIGFR94.W51, respectively.

Division Contact For Further Info: Paul J. Motise, HFD-323, 301-594-1089.

Inspection Guides Posted to New DFI BBS

The Division of Field Investigations has established a new bulletin board to distribute electronic documents. The board can be reached at 301-443-2893, at settings of 8 data bits, 1 stop bit, no parity, and speeds up to 14,400 bps. The BBS supports a suite of popular file transfer protocols, including Kermit, and Xmodem.

Among the current offerings are ASCII and WordPerfect 5.1 formats of the Inspection Guides to: Bulk Pharmaceutical Chemicals (9/91), High Purity Water Systems (7/93), Lyophilization of Parenterals (7/93), Microbiological Pharmaceutical Quality Control Laboratories (7/93), Pharmaceutical Quality Control Laboratories (7/93), Validation of Cleaning Processes (7/93), Dosage Form Drug Manufacturers - CGMP's (10/93), Liquid Injectable Radiopharmaceuticals Used in Positron Emission Tomography (PET) (11/93), Oral Solid Dosage Forms Pre/Post Approval Issues for Development and Validation (1/94), Sterile Drug Substance Manufacturers (7/94), Topical Drug Products (7/94), and Oral Solutions and Suspensions (8/94).

DFI Information Contact: Tom Johnson, HFC-132, 301-443-3340

P. Motise 11/10/94
DOC ID CNOTESW6.D94

1994 Subject Index for Human Drug CGMP NOTES

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-323
FAX: 301-594-2202 (Phone 301-594-1089)

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This FAX consists of this page plus _____ page(s).

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__not very; __ somewhat; __ very; __ extremely informative, and

__not very: __ somewhat; __ very; __ extremely useful to my inspectional/compliance activities.

Please have the information contact person get in touch with me regarding:

Sterilizing Filters ___ Stability Issues ____
Environmental Cross Contamination Controls ___
Electronic Records/Electronic Signatures ___ DFI Bulletin Board ___
Medical Gases ___ CGMP Labeling Controls ___
Other _____

Future editions of HUMAN DRUG CGMP NOTES should address the following CGMP questions/issues:

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